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REVIEW ARTICLE

Adjuvant partial breast radiotherapy for early breast cancer- ready for a change?

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Summary

Partial breast radiotherapy (PBRT) has recently gained an optional place as local adjuvant treatment after breast-conserving surgery (BCS) for selected early-stage breast cancer. With high-dose-rate (HDR) interstitial multicatheter brachytherapy (BT) performed under strict quality assurance criteria, there is level B evidence derived from one single randomized study with follow-up longer than 5 years and level C from several mature prospective non-randomized studies. For intra-lumpectomy cavity Mammosite HDR-BT and for external beam RT, as well as 3-dimensional (3D)-conformal or intra-operative therapy by electrons or photons, there is only level D evidence with no mature enough prospective data. Large phase III trials are ongoing for each PBRT technique, but their results might offer a level A evidence no earlier than 5 years.

Key words: brachytherapy, breast cancer, conformal radiotherapy, intraoperative irradiation, partial breast irradiation

Introduction

In USA and Europe, the standard of care in most women with early breast cancer (stages T1/T2, N0/N1a) is BCS plus whole breast radiotherapy (WBRT) with or without boost, which is preferable to total mastectomy because it provides survival equivalence while preserving the breast.

In the last few years, an alternative approach has been proposed, PBRT, which could be defined as delivery of radiotherapy to the lumpectomy cavity plus 1-2 cm margin after BCS in patients with early-stage breast cancer.

The rationale of PBRT is based on the assumption that microscopic tumor rarely extends 2 cm beyond the initial resection cavity, when margins are truly negative (more than 2 mm free margin in every direction) on final pathologic examination.

The potential advantages of PBRT over WBRT could be:

a) Shorter treatment duration, which may increase the probability for some patients to be treated with breast conservation, as a number of patients fail to receive radiation therapy after a BCS for invasive breast cancer because of its 4-6 weeks inconvenience.

b) Decreased acute and chronic toxicity by less dose to the lung, heart, skin and opposite breast and a more homogeneous dose to the target, difficult to achieve for big breasts.

c) Reduced costs for patient and/or the community.

Partial breast irradiation techniques

There are several modalities of PBRT:

I. Brachytherapy (BT)
   1. Interstitial BT
      a) Multi-catheter BT, HDR (e.g. 32-38.5 Gy/ 8-10 fr, 2 fr/day, 4-5 days).
      b) Multi-catheter BT, low-dose rate (LDR) (e.g. 45-50 Gy in 3-5 days).
   2. Intracavitary BT: Balloon HDR BT (MammoSite®) - similar schedule to 1a).

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II. 3-D conformal external beam RT (3DCRT).
   a) Classic schedule: 50 Gy/25fr/5 weeks ± "boost" 10 – 16 Gy/5-8fr/1-2 weeks.
   b) Accelerated, hypofractionated – same range of dose/fraction as HDR BT.

III. Intraoperative radiotherapy (IORT)
   a) Low energy photons (Intrabeam).
   b) Electrons.

Pathology studies published about extensions of the breast tumors are poor [1, 2] and cannot definitively answer the question whether PBRT adequately irradiates the volume of breast tissue at risk for local recurrence. Only phase III randomized trials of WBRT vs. PBRT could provide level A evidence regarding the equivalence of these two techniques.

Elsewhere failures (EF) are defined clinically as tumor in a different quadrant, which might be either a recurrence or a new breast cancer, the first one carrying a worse prognosis than the second one. Recently, Vicini et al. [3] proved that molecular clonality assays allow to clearly distinguishing between this two entities: in their series 83 % of EF were actually local recurrences.

Based on the clinical definition of the EF, several prospective, non-randomized trials obtained EFs rates of around 3% at 5-10 years of follow-up after wide excision alone (Table 1) [4-7].

In randomized trials comparing BCS with BCS + WBRT (Table 2), the EF overall rate is in the same range, although there are conflicting results, but the differences are not statistically significant [8-12].

It is interesting to note that the percentage of EFs in the above studies is similar to that of contralateral breast cancers, of about 3- 4 %, irrespective of adjuvant RT or not.

The strongest data supporting the use of PBRT comes from many prospective non-randomized trials [3,13-24] and from a single positive randomized trial [25] on this approach (Table 3).

Brachytherapy (BT)

One of the first phase I trials on LDR multi-catheter brachytherapy (Guy's Hospital, London) [13] showed a poor outcome, with high rates of local failure (37%). This trial was criticized, because of the lack of quality assurance of the brachytherapy implant, thus probably inadequate coverage of the target volume.

The longest follow-up (median 6 years) for a multi-institutional trial (RTOG 95-17) has been recently reported, favoring the HDR arm with 3 % in breast recurrences and 4% grade (G) 3-4 RTOG/ EORTC late effects comparing to 6 % recurrences and 18% G 3-4 toxicity in the LDR group [18].

The largest and most mature study with PBRT using the multi-catheter technique was conducted at the William Beaumont Hospital [3] and included 199 women, 120 treated with LDR technique, and 79 with HDR. At a median follow-up of 8 years, 6 women had experienced in-breast true recurrences, translating into 5-year and 10-year recurrence rates of 1.6% and 3.8%, respectively. The cosmetic result was good or excellent in 95-99% of the cases.

Table 1. Wide excision alone trials (prospective, non-randomized)

Institution [Reference]	*No. of patients*	*Follow-up interval (mo)*	*EF (%)*
Joint Center for Radiation Therapy, Boston, USA [4]	87	56	3.4
University of Miami, Miami, FL, USA [5]	67	80	3.0
Princess Margaret Hospital, Canada [6]	374	120	2.1
Tokyo Women's University, Japan [7]	82	72	3.6

EF: elsewhere failure, mo: months

Table 2. Randomized trials: conservative surgery vs. same surgery and adjuvant whole breast radiotherapy

Institution/Trial [Reference]	*No. of patients*	*Follow-up interval (mo)*	*EF*			
			BCS only		*BCS+ WBRT*	
			Crude	*%*	*Crude*	*%*
Ontario [8]	837	43	15/421	3.5	4/416	0.9
Milan III [9]	579	109	8/280	2.8	2/299	0.6
NSABP B06 [10]	1265	144	17/636	2.7	24/629	3.8
Uppsala-Orebro [11]	381	33	3/194	1.5	1/187	0.5
Finland [12]	152	80	4/72	5.5	4/80	5.0

EF: elsewhere failure, BCS: breast-conserving surgery, WBRT: whole breast radiotherapy, mo: months

Table 3. Studies on partial breast radiotherapy

Institution/Trial [Reference]	*No. of patients*	*Follow up (mo)*	*RT scheme*	*Failures*		
				Total (%)	*Tumor bed (%)*	*EF (%)*
Phase I-II Brachytherapy Trials						
Guy's Hospital I [13]	27	72	LDR 55 Gy/ 5 days, 40 cGy/h	37	–	–
Guy's Hospital II [14]	50	60	MDR Cs(137) 45 Gy in 4 daily fractions of about 6 h each	18	14	4
Virginia University Medical College [15]	44	42	HDR: 34 Gy/10 fr/5 days LDR: 45 Gy, 50 cGy/h	0	0	0
London Regional Cancer Center [16]	39	91	37.2 Gy in 10 fractions (b.i.d.)	16.2	6.2	10
Ochsner Clinic [17]	160	84	LDR 45 Gy/96 h or HDR 32 Gy/8fr/4 days, b.i.d	2.5	1.3	1.2
RTOG 95-17 [18]	33 LDR	73	LDR (45 Gy in 3.5-5 days) vs.	6	–	–
				vs.		
	66 HDR		HDR (34 Gy in 10 twice-daily fractions in 5 days)	3	–	–
University of Kansas [19]	25	47	LDR 20-25 Gy over 24-48 h	0	–	–
University of Pisa, Italy [20]	90	27	LDR 50-60 Gy	4.4	–	–
Massachusetts General Hospital [21]	48	23	LDR 50 Gy or 55 Gy or 60 Gy, 50 cGy/h	0	0	0
Tufts/Brown Universities [22]	33	58	HDR 3.4 Gy/fraction, b.i.d, 5 days, to a total dose of 34 Gy	6	0	6
National Institute of Oncology, Hungary [23,24]	45	80	HDR 30.3 Gy (n=8) and 36.4 Gy (n=37) in 7 fractions within 4 days	6.7	0	6.7
William Beaumont Hospital [3]	120	82	120 pts (60%): LDR 50 Gy over 96 h at 0.52 Gy/h	3.8	1.9	1.9
	79	39	79 pts (40%): HDR 32 Gy/8 fr (separated by 6 h; 71 pts) or 34 Gy/10 fr (8 pts)			
Phase III Brachytherapy Trial						
National Institute of Oncology, Hungary [25]	258	66	50 Gy WBRT (n=130) vs. PBRT (n=128). The latter consisted of either	3.4		
				vs.		
			7×5.2 Gy HDR-BT (n=88) or 50 Gy electron RT (n=40)	4.8	2.4	2.4
Phase I- II 3D CRT						
William Beaumont Hospital [26]	31	10	34 or 38.5 Gy/10fr b.i.d	0	0	0
New York University Hospital [27]	47	18	30 Gy/5fr/10 days	0	0	0
Phase III External Beam RT						
Christie Hospital [28]	353	65	40-42 Gy/8fr partial RT (e^-)	25.5	20	5.5
	355		45-50 Gy WBRT	10.5	8	2.5
Phase I- II IORT						
University College of London [29]	185	45	20 Gy at 1 mm;50 Kv	0.9	–	–
European Institute of Oncology [30]	237		Electrons 21Gy/ surface, 90 % reference isodose, 3 - 9 MeV	1.4	–	–

LDR: low dose rate, HDR: high dose rate, MDR: medium dose rate, Cs: caesium, fr: fraction, pts: patients, EF: elsewhere failure, PBRT: partial breast radiotherapy, WBRT: whole breast radiotherapy, BT: brachytherapy, CRT: conformal RT, IORT: intraoperative radiotherapy, mo: months, 3D CRT: 3-dimensional conformal radiotherapy, b.i.d: twice daily

Polgar et al. recently published their data of the single phase III randomized study with at least 5 years of follow-up, comparing PBRT to WBRT. There were no significant differences in terms of local recurrence (Table 3), overall/ cause-specific or disease-free survival at 5 years. Moreover, despite the fact that their HDR schedule was with higher dose/fraction than those used in the ongoing phase III trials (i.e. 5.2 Gy vs. 3.4-3.85 Gy) the cosmetic results favored PBRT, especially the HDR multicatheter technique (81.2 % excellent/good cosmesis vs. 65.5 % for 6-9 MV photons WBRT or 52.2 % for cobalt WBRT).

The major disadvantage of the multi-catheter technique is that the placement of interstitial applicators to adequately cover the tumor bed is a specialized skill requiring particular training and is very operator-dependent. The placement of surgical metallic clips on the lumpectomy cavity walls is the best way to guide the target volume delineation for PBRT, although ultrasound or CT scan are also valuable. Doing the BT implant preoperatively, with the open cavity (Figure 1), allows direct visualization of the target volume, but exposes to the risk of an useless procedure if the final pathologic report does not fulfill all criteria for patient selection for BT. Nevertheless, in some cases, the implant may be used as a "boost" to the whole breast irradiation (WBI).

An easily reproducible brachytherapy technique is with the MammoSite® 4-6 cm spherical or elliptical dual lumen balloon-catheter, inflated in the lumpectomy cavity with 35-70 cc of saline. The HDR Iridium 192 source is afterloaded via the catheter in the balloon center, giving a simple isotropic spherical distribution of isodoses (Figure 2). On the CT planning (Figure 3), the skin-balloon surface distance should exceed 5 mm (ideally ≥ 7 mm) without evident air, seroma or hematoma interpose between the surgical cavity and MammoSite outer wall in order to ensure an acceptable implant, as the dose is prescribed at 1 cm from the surface of the balloon, usually 34 Gy/ 10 fr / 5 days, b.i.d. It is estimated that over 10,000 patients worldwide have been treated with MammoSite, but the follow up is too short to allow reliable conclusions. Nevertheless, comparing with multicatheter BT, a recurrence rate of 1-1.5% at 18 months is higher, the cosmetic result is poorer and the geometry of the implant is much often suboptimal (leading to canceling of the procedure, with MammoSite take off in up to 50% of cases).

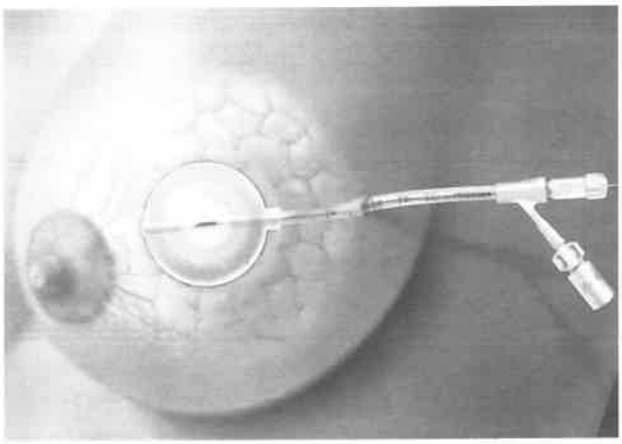


Figure 2. MammoSite balloon inflated in place.

Three dimensional conformal external beam radiotherapy (3D CRT)

Target definition is like in any postoperative 3D CRT: the gross tumor volume (GTV) is the lumpec-

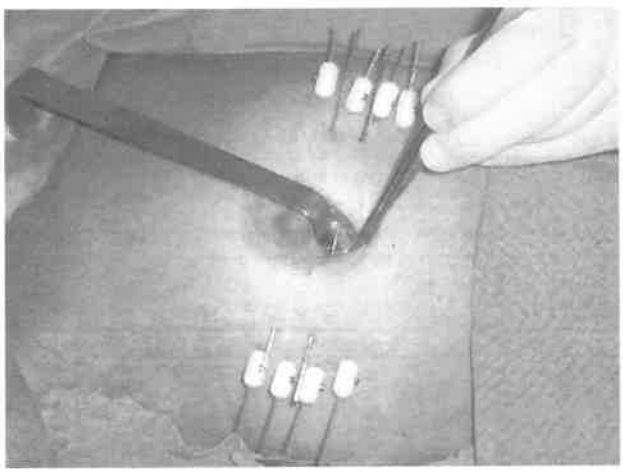


Figure 1. Interstitial preoperative multicatheter brachytherapy with equidistant parallel plastic tubes secured to the skin replacing stainless needles.

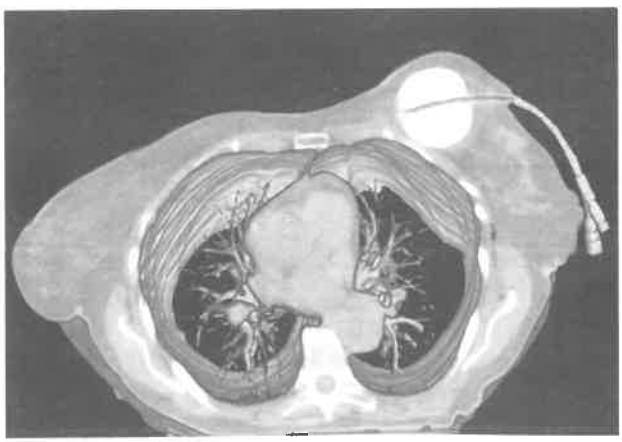


Figure 3. Dosimetric scan for MammoSite.

tomy cavity, the clinical target volume (CTV) is expanded in each direction with 2 cm minus the amount of clean surgical margin in that direction (e.g. if the pathology describes 6 mm lateral and 9 mm medial, the extra-margins for CTV will be 14 mm lateral and 11 mm medial), with adjustments for the outer margin of the thoracic wall and the inner contour of the skin. An additional margin is generated for the planning target volume (PTV) taking into account the respiratory movements and the uncertainties due to daily positioning of the patient. The isocenter is defined according ICRU criteria in the midpoint of the GTV and multiple isocentric fields are set up to homogeneously cover the PTV and maximally spare the lung, heart, skin and contralateral breast by using multileaf collimators.

The potential advantages of a 3D CRT compared to brachytherapy include:

a) Improved dose homogeneity within the target volume and, therefore, a likely better cosmetic outcome.

b) Elimination of an additional invasive procedure may reduce complication rates and cost.

c) Use of same facilities as for classic radiotherapy.

This technique has the shortest follow-up (12-18 months) compared to other PBRT methods, with published results [26,27] on less than 100 patients (Table 3). Therefore, a 100% control rate and 100% good to excellent cosmetic result are promising but certainly there is a need for longer follow-up to gain proper reliability.

Partial non-conformal external beam radiotherapy

The only published phase III trial comparing external beam WBRT and PBRT is the study performed at Christie Hospital in Manchester, England [28]: 708 women with breast cancer < 4 cm were randomized to receive either whole breast and regional nodal RT (WBRT) or PBRT. No systemic therapy was given. With a median follow-up of 65 months, the actuarial breast recurrence rate (first event) is 15% (PBRT) vs. 11% (WBRT) for infiltrating ductal carcinoma, whereas for infiltrating lobular carcinoma the recurrence rate was 34% (PBRT) vs. 8% (WBRT). A high actual recurrence rate of 21% (PBRT) and 14% (WBRT) was also found for extensive ductal carcinoma *in situ*, which are nowadays established contraindications for PBRT. The high rate of recurrence was also attributed to the suboptimal PBRT technique with direct electron field, obviously inhomogeneous.

Intraoperative radiotherapy (IORT)

The main advantage of IORT is the ability to administer the entire therapeutic dose of breast RT at the time of surgery to the tissue at greatest risk of cancer recurrence, as surgical margins are mobilized and conformed with sutures to the applicator shape. This avoids the possibility of a "geographical miss" sometimes occurring with the target definition in postoperative RT [29]. The major disadvantage is that the margins and nodal status are not known before delivery of IORT.

Whether with single fractions of 21 Gy by cone-shaped electron beam (Figure 4) or 20 Gy by low-energy photons by spherical applicator (Figure 5), the biologic equivalent dose is of 60 Gy/ 6 weeks. The Milan team reported a 1.5 % ipsilateral recurrence and 2.5 % late toxicity on their 237 patients' series, with a median follow-up of 19 months [30].

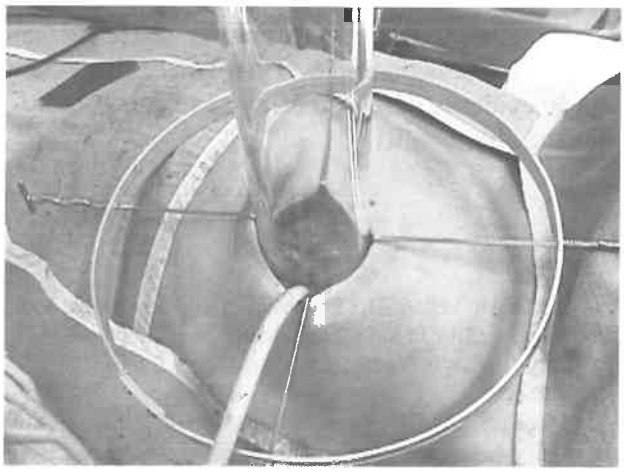


Figure 4. Intraoperative electron radiotherapy.

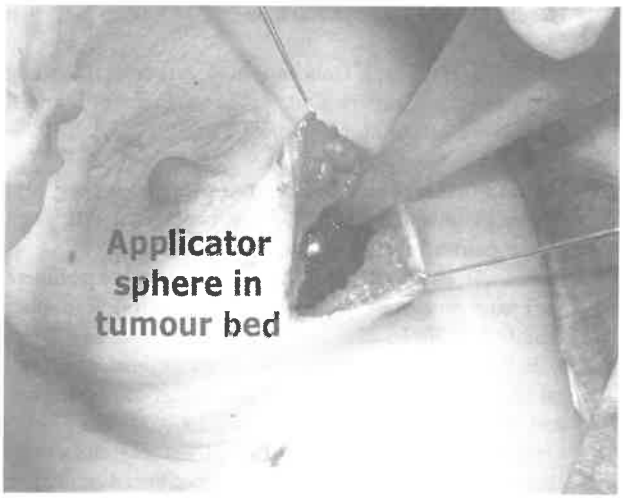


Figure 5. Intraoperative photon radiotherapy.

Conclusions

The only long-term data sustaining adjuvant partial breast irradiation (APBI) come from studies of the multi-catheter technique, with same recurrence rates as WBRT, better cosmetic outcome and shortened treatment time, therefore in the benefit of the patient.

It is very unlikely that insignificant differences in local recurrences will translate into significant overall survival improvements, but – from at least from a theoretical point of view - allowing earlier onset of systemic therapy (Tamoxifen for example, which usually starts only after the completion of the external WBRT) may be more useful for microscopic metastatic disease. Until the results of two major phase III trials, launched in 2006 by RTOG in USA and EORTC in Europe, we believe that there is good evidence-based data to support rigorous quality assured HDR multicatheter APBI as option for properly selected early breast cancer i.e. age more than 50 years, pT1- pT2 less than 3 cm, invasive or *in situ* ductal carcinomas without lobular or extensive *in situ* component, clean margins larger than 5 mm, pN0 on sentinel or level I/II axillary's dissection and no evidence of multifocality on imaging studies, including breast MRI.

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